Surgery for Neck Recurrence of Differentiated Thyroid Cancer: Outcomes and Risk Factors

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Background: Persistent/recurrent disease in the neck is frequent in patients with differentiated thyroid cancer (DTC).

Objective: Assess efficacy, safety, and prognostic factors of first neck reoperation in DTC.

Methods: Retrospective study of consecutive patients undergoing neck reoperation for recurrent/persistent DTC in a referral cancer center. Response after reoperation was defined according to the 2015 American Thyroid Association guidelines.

Findings: One hundred sixty-one DTC patients were enrolled (64% females, median age 35 years, 96% papillary DTC). Initial stage was pT3 in 43% and pT4 in 10%, pN1 in 74%. Aggressive histology was present in 25% of the patients, in both primary and persistent/recurrent tumor. Four patients had no malignancy in the reoperative specimen, and 1 patient died due to postoperative hematoma and was excluded from further analysis. Following reoperation, 15 patients (10%) had persistent structural disease, 16 (10%) had biochemical incomplete response, 26 (17%) had indeterminate response, and 99 (63%) had complete response (CR), among whom 24 relapsed later. After a median follow-up of 5 years, only 83 patients (53%) had CR without the need for further treatments. The rate of permanent complications was: hypoparathyroidism 2%, laryngeal nerve palsy 0.6%, other 6%. Age ≥45 years, aggressive histology, and lymph node ratio ≥0.6 at initial surgery were independent risk factors for incomplete response after reoperation. Male sex, aggressive histology, and ≥10 metastases at reoperation were independent risk factors of secondary relapse following CR achieved with reoperation.

Conclusion: A careful risk-benefit analysis should guide surgical decision, particularly in patients with risk factors for incomplete response. (***J Clin Endocrinol Metab*** **102: 1020–1031, 2017)**

The main concern in follow-up for differentiated thyroid cancer (DTC) is locoregional recurrence that can occur in up to 75% of high-risk patients (1).

Once a suspicious lesion in the neck is found, clinicians should determine whether follow-up can be maintained or whether an active treatment is indicated. Observational studies have shown that selected abnormal thyroid bed lesions and neck lymph nodes detected on neck ultrasonography can be safely managed with simple follow-up (2–4). Neck lesions should be submitted to fine-needle aspiration only if an abnormal finding will result in active treatment (1, 5).

To date, surgery is the treatment of choice for locoregional perisitent/recurrent DTC (1). Previous studies suggested

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Abbreviations: ATA, American Thyroid Association; BIR, biochemical incomplete response; CI, confidence interval; CR, complete response; CT, computed tomography; DTC, differentiated thyroid cancer; ECE, extracapsular extension; IndR, indeterminate response; LNR, lymph node ratio; OR, odds ratio; FDG-PET, fluorodesoxyglucose positron emission tomography; PTC, papillary thyroid cancer; RAI, radioiodine; SIR, structural incomplete response; Tg, thyroglobulin; TgAb, thyroglobulin antibody; TSH, thyrotropin; WBS, whole-body scan.

that 19% to 71% of patients can achieve a complete response (CR) after additional surgery, but heterogeneous criteria have been used to define outcomes (6–21). When serum thyroglobulin (Tg) was considered for the definition of outcome, various cut-offs have been used. Outcome was defined based on Tg normalization alone in 4 studies, resulting in a CR in 17% to 51% of patients (11, 13, 15, 16). In 2 studies only absence of disease on neck imaging was considered (structural disease), resulting in a CR in 72% to 100% of patients (17, 21).

The main goal of this study was to evaluate the efficacy of the first reoperation performed in a tertiary cancer center for recurrent/persistent disease following initial treatment of DTC and to evaluate prognostic factors for incomplete response to treatment, defined according to the latest American Thyroid Association (ATA) 2015 guidelines (1). Other goals were to assess long-term efficacy of reoperation according to the ATA 2015 treatment efficacy criteria applying the concept of dynamic risk stratification and to explore prognostic factors for death from thyroid cancer.

Patients and Procedures

Patients

Patients included met the following criteria: 1) first reoperation with a curative intent for recurrent/persistent DTC; 2) initial treatment, including total thyroidectomy with or without neck dissection; 3) reoperation performed for non–radioiodine (RAI)-avid relapse independently of size or for RAI-avid relapse of ≥1 cm or more; 4) no evidence of distant metastasis at the time of reoperation; 5) assessment of cure by serum Tg and neck imaging; and 6) follow-up of at least 6 mo or until patient's death.

Approval from our Institutional Review Board was obtained for the study. Records of the 207 consecutive patients who underwent first reoperation at Gustave Roussy between July 1995 and March 2013 for neck relapse were reviewed. Forty-six patients were referred to Gustave Roussy only for surgery and were then followed up in other centers. The study population was formed by 161 patients who met the inclusion criteria (Fig. 1).

Initial characteristics and primary treatment

The presence of clinical disease (palpable lymph nodes, dysphonia, and/or dysphagia) at the time of DTC diagnosis, exposure to radiation in childhood, and familial thyroid cancer history (at least 2 first-degree relatives with DTC) were recorded. For all patients, primary treatment consisted of total thyroidectomy (with 1 or 2 procedures) with or without neck dissection, followed by RAI ablation. Neck dissection was defined as "prophylactic" when performed in the absence of abnormal lymph nodes on preoperative imaging and "therapeutic" in cases of abnormal neck lymph nodes on preoperative imaging or on intraoperative clinical examination (22). Dissected compartments were listed as ipsilateral or contralateral to the primary tumor or to the larger tumor for bilateral cancers.

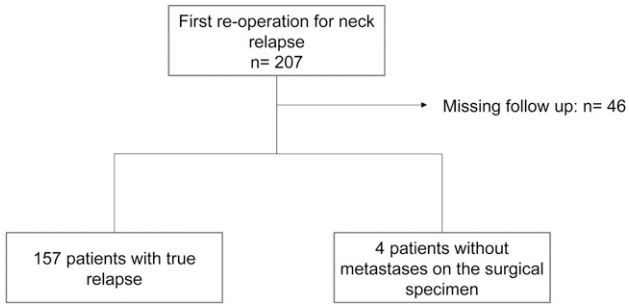

Figure 1. Population selection.

Lymph node neck compartments were classified into 7 levels (I to VII) (22, 23).

Follow-up

After primary treatment and reoperation, patients were followed every 3 to 12 months with physical examination, serum Tg measurement under LT4 therapy (Tg/T4) or after thyrotropin (TSH) stimulation (Tg/TSH) following hormone withdrawal or recombinant human TSH administration and imaging, including at least 1 of the following techniques: neck ultrasonography, RAI whole-body scan (WBS), computed tomography (CT) with contrast agent or fluorodesoxyglucose positron emission tomography (FDG-PET)/CT.

Disease status was determined after primary treatment, after reoperation, and at last assessment. Disease status was either: 1) CR, defined by a serum Tg/LT4 and/or a Tg/TSH ≤1 ng/mL in the absence of anti-Tg antibodies (TgAbs) with normal neck imaging; 2) biochemical incomplete response (BIR), defined by a serum Tg/LT4 >1 ng/mL or a Tg/TSH ≥10 ng/mL in the absence of TgAbs with normal neck imaging or by persistent or increasing TgAbs with normal neck imaging; 3) structural incomplete response (SIR), defined by abnormal neck imaging; or 4) indeterminate response (IndR), defined by either a serum Tg/TSH >1 and <10 ng/mL and/or decreasing TgAbs, and/or the presence of nonspecific imaging abnormalities.

Recurrent disease refers to a patient who achieved CR after initial treatment and who had structural disease afterward.

Reoperation

Reoperation was performed by either J.-P.T., D.M.H., or H.M. Surgical indications were discussed in the institutional multidisciplinary thyroid board meeting. Surgical procedure was en bloc compartment-oriented neck dissection or focused dissection in case of recurrence in a previously dissected compartment. When reoperation was performed in previously dissected compartments or in the case of small lesions, localizing procedures such as per-operative ^{131}I-guided surgery and charcoal tattooing were used (24, 25). All reoperation specimens were examined by 2 experienced pathologists (Bernard Caillou and A.A.).

Incidences of the following complications were analyzed: hemorrhage, wound infection, chronic neck pain (*i.e.*, need of specialized care and/or level 2 painkillers for ≥6 months), permanent hypoparathyroidism (*i.e.*, treatment with calcium and vitamin D supplementation for ≥6 months), and permanent laryngeal nerve or spinal accessory nerve palsy (*i.e.*, the persistence of laryngeal paralysis at laryngoscopy or clinical

trapezius dysfunction for ≥6 months). Patients who were already hypoparathyroid before the reoperation and patients with recurrent nerve paralyses following voluntary resection due to macroscopic nerve invasion were recorded but not included in the reoperation complication rate.

Measurement of Tg levels

From 1995 until 2005, serum Tg was measured using an immunoradiometric assay (SELco Tg; Medipan Diagnostica, Selchow, Germany). The functional sensitivity was 0.9 ng/mL, and Tg level was considered as not accurately measured when the routine recovery test (performed in all samples) was <80%. From 2006 onward, Tg was measured using a chemiluminescent immunoenzymatic "sandwich" assay (Access Tg, automated on UniCel DxI 800 instruments; Beckman Coulter, Villepinte, France) with an functional sensitivity of 0.1 ng/mL. The Tg level was considered as not accurately measured in the presence of TgAbs with the Access TgAb II assay (Beckman Coulter) (26).

Statistical analysis

Categorical variables were expressed as number and percentage, continuous variables as median and range. Risk factors for persistent disease at first and last assessment were analyzed by univariate and multivariate logistic regression and included the following characteristics: sex, age, histology, tumor size, multifocality, extrathyroidal extension, number of metastatic nodes (N1) (≤10 *vs* >10), number of metastatic nodes with extracapsular extension (ECE-N1) (≤3 *vs* >3), size of the largest metastatic node at primary surgery and at reoperation, lymph node ratio (LNR; ratio of the number of metastatic lymph nodes/total number of resected lymph nodes) (<median *vs* ≥median), relapse in a previously dissected area, Tg value at relapse assessment (<10 ng/mL *vs* ≥ 10 ng/mL), overall number of N1 (sum of N1 resected at primary surgery and reoperation) (≤10 *vs* >10), and overall number of ECE-N1 (sum of ECE-N1 resected at primary surgery and reoperation) (≤3 *vs* >3). Variables associated with persistent disease with a *P* value of <0.10 in the univariate analysis were included in the multivariate regression analysis.

Risk factors associated with thyroid cancer mortality were analyzed on univariate analysis and included age, sex, histology, relapse size, and RAI refractory disease.

All reported *P* values were 2 sided and the significance level was 0.05. The odds ratio (OR) together with 95% confidence interval (CI) were reported. Analyses were performed using SAS statistical software (SAS Institute, Cary, NC).

Results

Initial characteristics

For the population selection, see Fig. 1. The clinical characteristics of the 161 patients (64% females; median age, 35 years) are reported in Table 1. All patients underwent total thyroidectomy, with 1 surgical procedure in 138 (86%) and with 2 procedures in 23 (14%) cases. Neck dissection was performed in 115 cases (71%), with therapeutic neck dissection in 43% of patients. Histologic types were papillary thyroid cancer (PTC) in 154 (96%)

Table 1. Initial Characteristics and Primary Treatment

Characteristics	N = 161 Patients (%)
Male/female	58 (36%)/103 (64%)
Median age at diagnosis, y	35 (7–82)
Previous radiation exposure	3 (2%)
Familial thyroid cancer[a] (n = 148 patients)	10 (7%)
Clinical disease at diagnosis[b] (n = 137 patients)	60 (44%)
Neck dissection at primary surgery	
Yes, prophylactic	29 (18%)
Yes, therapeutic	69 (43%)
Yes, surgical intent unknown	17 (10%)
No	46 (29%)
Central compartment dissection	
No	59 (36%)
Ipsilateral	53 (33%)
Bilateral	43 (27%)
Central compartment dissected, side unknown	6 (4%)
Lateral compartment dissection	
No	75 (47%)
Ipsilateral	60 (37%)
Bilateral	24 (15%)
Contralateral	2 (1%)
Histology	
PTC including aggressive subtype[c]	154 (96%)
FTC	5 (3%)
Poorly differentiated	2 (1%)
Median tumor size, mm (n = 148 patients)	20 (3–90)
Tumor foci	
Unifocal	63 (39%)
Multifocal unilateral	22 (14%)
Multifocal bilateral	62 (38%)
Multifocal not otherwise specified	6 (4%)
Not available	8 (5%)
Extrathyroidal extension	
No	73 (46%)
Microscopic	65 (40%)
Macroscopic	16 (10%)
Not available	7 (4%)
pT at initial diagnosis	
pT1a	23 (14%)
pT1b	28 (17%)
pT2	18 (11%)
pT3	68 (43%)
pT4	16 (10%)
pTx	8 (5%)
pN at initial diagnosis	
N1	119 (74%)
N0	4 (2%)
Nx	38 (24%)
Median number of N1 (n = 113 pts)	4 (1–46)
Patients with N1-ECE (n = 94 patients)	40 (43%)
Median number of N1-ECE (n = 38 patients)	2 (1–17)
Median number of nodes dissected (n = 112)	11.5 (1–105)
LNR at primary surgery	0.6 (0.06–1)

[a] At least 2 first-degree relatives were affected from thyroid cancer of follicular origin.

[b] Presence of clinical findings due to thyroid cancer (palpable lymph nodes, dysphonia, dysphagia).

[c] Aggressive PTC variants include insular variant in 5, tall cell variant in 14, oxyphilic variant in 1, and sclerosing variant in 18.

and follicular thyroid cancer in 5 (3%). An aggressive histology was observed in 40 cases (25%), aggressive PTC subtypes in 38 cases (insular variant in 5, tall cell variant in 14, oxyphilic variant 1, and diffuse sclerosing variant in 18), and poorly differentiated thyroid cancer in 2 cases. Initial N status was pN1 in 119 (74%) cases (39% N1a and 61% N1b).

Following initial surgery, 23 patients (14%) had permanent hypoparathyroidism and 21 (13%) had unilateral permanent laryngeal paralysis. RAI ablation was performed in 160 patients (99%) and the postablation WBS showed abnormal foci of RAI uptake outside the thyroid bed in 57 cases. Following initial treatment, disease status was CR in 14 (9%), BIR or IndR in 30 (19%), SIR in 112 (70%), and status was not evaluable in 5 patients. Recurrent disease of the 14 patients initially classified as CR occurred after a median time of 5 years (8 months to 33 years).

Recurrent/persistent disease assessment

Recurrent/persistent disease was evident on preoperative imaging in all patients and was detected with neck ultrasonography in 129 cases, and with other techniques (posttherapy WBS, FDG-PET/CT, CT) in 32 cases. A median of 2 lesions per patient were detected (range, 1 to 12) with a median size of the largest lesion of 15 mm (range, 4 to 53). Suspicious lesions were located in neck areas not previously dissected in 66 patients (41%), in previously dissected areas in 70 (43%) patients, and in both dissected and not previously dissected areas in

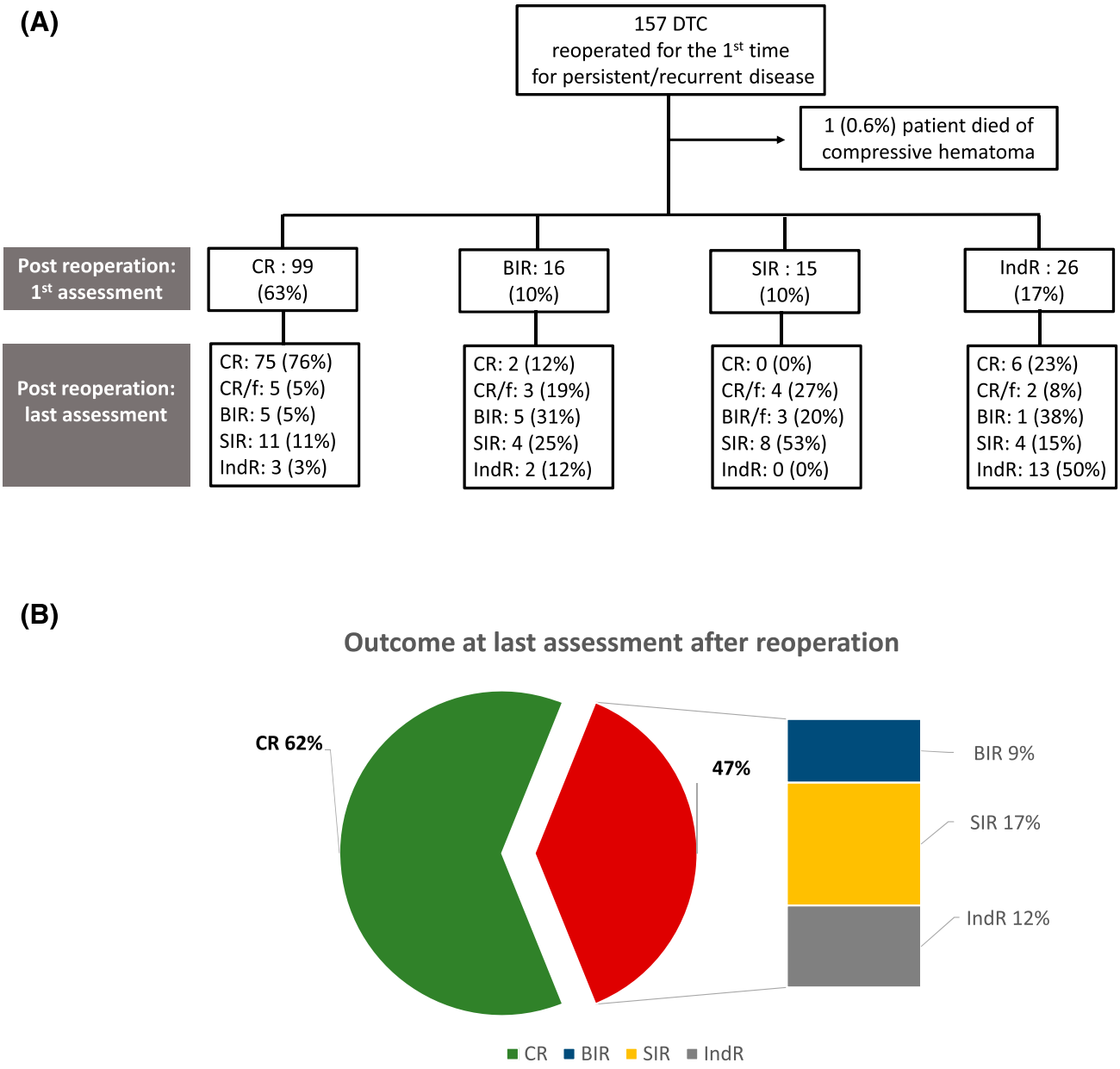

Figure 2. Response to reoperation at first postoperative (A) and last assessment (A and B) according to each response to treatment category.

Table 2. Risk Factors for BIR or SIR or Ind (Absence of CR) at First Postreoperation Assessment

Variable	BIR + SIR + Ind/ All Patients [N = 57/156 (%)]	Univariate Analysis OR (95% CI)	*P*	Multivariate Analysis OR (95% CI)	*P*
Age					
<45 y	33/106 (31)	1		1	
≥45 y	24/50 (48)	2.0 (1.0–4.0)	0.04	6.2 (1.7–22.7)	0.005
Sex					
Female	28/101 (28)	1		1	
Male	29/55 (53)	2.9 (1.5–5.9)	0.002	2.4 (0.7–7.3)	0.13
Clinical disease at diagnosis					
No	27/74 (36)	1			
Yes	20/58 (34)	0.9 (0.4–1.9)	0.59		
Unknown	10/24 (42)	1.2 (0.5–3.2)	0.56		
Surgical intention of initial surgery					
Prophylactic	10/27 (37)	1			
Therapeutic	25/67 (37)	1.0 (0.4–2.9)	1		
Unknown	22/62 (35)	0.9 (0.3–2.7)	1		
Aggressive histology					
No	35/117 (30)	1		1	
Yes	22/39 (56)	3.0 (1.4–6.4)	0.003	4.9 (1.6–15.2)	0.005
Tumor size					
≤20 mm	27/86 (31)	1			
21–40 mm	19/44 (43)	1.6 (0.8–3.5)	0.65		
>40 mm	6/13 (46)	1.8 (0.6–6.1)	0.52		
Unknown	5/13 (38)	1.1 (0.3–4.1)	0.62		
Multifocal					
No	23/60 (38)	1			
Yes	31/88 (35)	0.8 (0.4–1.7)	0.79		
Unknown	3/8 (38)	1.0 (0.2–4.8)	0.96		
Bilateral					
No	31/86 (36)	1			
Yes	24/60 (40)	0.8 (0.4–1.7)	0.62		
Unknown	2/10 (17)	0.5 (0.1–5.5)	0.43		
Extrathyroidal invasion					
No	24/71 (34)	1			
Yes	30/78 (38)	1.2 (0.6–2.4)	0.55		
Unknown	3/7 (43)	1.9 (0.4–9.3)	0.57		
Number of N1 at primary surgery (n = 110)					
≤10 N1	22/78 (28)	1		1	
>10 N1	17/32 (53)	2.9 (1.2–6.7)	0.01	1.6 (0.5–5.2)	0.40
Number of N1 with ECE at primary surgery (n = 38)					
≤3	7/24 (29)	1			
>3	7/14 (50)	2.4 (0.6–9.5)	0.20		
LNR at primary surgery (n = 102)					
<0.6	11/49 (22)	1		1	
≥0.6	25/53 (47)	3.1 (1.3–7.3)	0.01	4.8 (1.5–15.8)	0.009
Tg before reoperation (n = 148)					
<10 ng/mL	23/79 (29)	1		1	
≥10 ng/mL	30/69 (59)	1.9 (0.9–3.7)	0.07	2.3 (0.7–6.9)	0.14
Relapse in previously dissected area					
No	20/63 (32)	1			
Yes	27/68 (40)	1.4 (0.7–2.9)	0.63		
Both (dissected and not dissected)	10/25 (40)	1.4 (0.6–3.7)	0.67		
Relapse size					
≤10 mm	10/28 (36)	1			
>10 mm	21/50 (42)	1.3 (0.5–3.4)	0.20		
Not applicable	21/78 (27)	0.7 (0.3–1.7)	0.12		
RAI refractory					
No	25/65 (38)	1			
Yes	32/91 (31)	0.9 (0.4 –1.7)	0.67		
Number of N1 at reoperation					
≤10 N1	48/141 (34)	1		1	
>10 N1	9/15 (60)	2.9 (0.97–8.6)	0.05	3.0 (0.6–17.4)	0.19

(*Continued*)

Table 2. Continued

Variable	BIR + SIR + Ind/ All Patients [N = 57/156 (%)]	Univariate Analysis OR (95% CI)	P	Multivariate Analysis OR (95% CI)	P
Number of N1-ECE at reoperation					
≤3	45/132 (34)	1			
>3	11/23 (43)	1.7 (0.7–4.3)	0.20		
LNR at reoperation					
<0.17	20/72 (28)	1		1	
≥0.17	37/84 (41)	2.0 (1.01–4.1)	0.04	1.2 (0.4–3.8)	0.77

Clinical disease is indicated by the presence of clinical findings due to thyroid cancer (palpable lymph nodes, dysphonia, dysphagia).

25 patients (16%). Relapse in thyroid bed associated with lymph node relapse occurred in 4 patients. The central compartment was involved in 33 (20%) cases, the lateral compartment in 55 cases (34%, of which 10% were bilateral), both central and lateral compartments in 69 cases (44%, of which 23% were bilateral), and other compartments (*e.g.*, level VII) were involved in 4 cases (3%).

Before reoperation, basal Tg/LT4 level was elevated in the absence of TgAbs in 24 cases (median, 6.9 ng/mL; range, 1.1 to 61.8) and stimulated Tg/TSH was elevated in 80 cases (median, 28 ng/mL; range, 1.3 to 3582; stimulated with recombinant human TSH in 11 and thyroid hormone withdrawal in 69 cases). Serum Tg was <1 ng/mL in the absence of TgAbs in 22 cases (either on LT4 or after TSH stimulation). Detectable TgAbs were present in 15 cases (5 of which had elevated Tg values). Preoperative Tg values were not available in 20 patients.

Reoperation

Reoperations involved: 1) the central compartment in 137 (85%) patients (33 ipsilateral, 90 bilateral, and 14 contralateral); 2) the lateral compartment in 147 (91%) patients (63 ipsilateral, 73 bilateral, 11 contralateral), and 3) other compartments in 36 patients (level VII or the level I or others). Seventy-seven (57%) central compartment and 71 (49%) lateral compartment dissections were performed in already-dissected areas. In addition to lymph node dissection, surgery involved the resection of a thyroid bed relapse in 4 patients (2%). ^{131}I radio-guided surgery and charcoal tattooing were used in 93 (58%) and 18 (11%) patients, respectively.

Reoperation histology

Metastatic disease was found on pathologic specimen in all patients except 4. In 2 patients reoperation was performed based on suspicious findings on neck ultrasound and abnormal RAI uptake despite Tg/LT4 level <1 ng/mL, but the final pathology report demonstrated no malignancy (sarcoidosis in 1 and inflammatory lymph nodes in the other). In 2 patients, reoperation was performed based on suspicious cytology, but the final pathology report demonstrated benign lymph nodes. Among these 2 cases, serum Tg level was elevated in 1 case and was <1 ng/mL in the other. Tg level in the aspirate fluid, available in 1 case, was <0.1 ng/mL. At last assessment, 3 of these 4 patients had CR and 1 relapsed with non–RAI-avid lung metastases.

Among the 157 patients with resected metastatic disease, the median number of resected lymph nodes was 29 (range, 1 to 98), with a median number of N1 of 4 (range, 1 to 41). The median size of the largest N1, available in 78, cases was 14 mm (range, 4 to 70 mm). ECE-N1 were present in 88 patients; the median number of ECE-N1 was 2 (1 to 24). The median LNR was 0.17 (0.02 to 1).

Reoperation morbidity

Permanent complications due to the reoperation were as follows: 3 (2.1%) hypoparathyroidism; 1 (0.6%) unintentional unilateral laryngeal nerve palsy; and 10 (6.2%) others (hematoma in 3 cases, chronic pain in 3 cases, spinal accessory nerve paralysis in 2 cases, wound abscess in 1 case, and temporary tracheostomy in 1 case). There were 5 (3.1%) voluntary nerve recurrent resections due to macroscopic nerve invasion. One patient died of a compressive hematoma (reoperation mortality rate of 0.6%). This patient was excluded from further analysis.

Postreoperation disease status assessment of patients with histologically confirmed relapse

Following reoperation, first disease status assessment was performed after a median time of 7 months (range, 1 to 68). Patients were classified as CR in 99 (63%) cases, BIR in 16 (10%) cases, SIR in 15 (10%) cases, and as IndR in 26 (17%) cases. SIR was located in the neck in 11 and in distant sites in 4 patients and was detected on neck ultrasonography in 4 cases, on neck ultrasonography and FDG-PET/CT or neck and chest CT in 10 cases, and on WBS in 1 case.

Table 3. Risk Factors for BIR or SIR or Ind (Absence of CR) at Last Assessment

Variable	Persistent Disease/ All Patients [N = 59/156 (%)]	Univariate Analysis OR (95% CI)	*P*	Multivariate Analysis OR (95% CI)	*P*
Age					
<45 y	34/106 (32)	1		1	
≥45 y	25/50 (50)	2.1 (1.0–4.2)	0.03	1.9 (0.8–4.0)	0.11
Sex					
Female	27/101 (27)	1		1	
Male	32/55 (58)	3.8 (1.9–7.6)	0.0002	2.7 (1.3–5.9)	0.009
Clinical disease at diagnosis					
No	26/74 (35)	1			
Yes	25/58 (43)	1.4 (0.7–2.8)	0.30		
Unknown	8/24 (33)	0.9 (0.3–2.4)	0.60		
Surgical intention of initial surgery					
Prophylactic	10/27 (37)	1			
Therapeutic	28/67 (43)	1.2 (0.4–3.5)	0.82		
Unknown	21/62 (34)	0.9 (0.3–2.5)	0.81		
Aggressive histology					
No	36/117 (31)	1		1	
Yes	23/39 (59)	3.2 (1.5–6.8)	0.002	2.3 (1.0–5.2)	0.05
Tumor size					
≤20 mm	29/86 (34)	1			
21–40 mm	20/44 (45)	1.6 (0.8–3.4)	0.27		
>40 mm	5/13 (38)	1.3 (0.4–4.1)	0.93		
Unknown	5/13 (38)	1.3 (0.4–4.1)	0.93		
Multifocal					
No	19/60 (32)	1			
Yes	37/88 (42)	1.5 (0.7–3.1)	0.47		
Unknown	3/8 (38)	1.3 (0.3–6.0)	0.96		
Bilateral					
No	27/86 (31)	1		1	
Yes	30/60 (50)	2.1 (1.1–4.3)	0.02	1.8 (0.8–3.8)	0.10
Unknown	2/10 (20)	0.5 (0.1–2.7)	0.21	0.5 (0.1–3.0)	0.29
Extrathyroidal invasion					
No	24/71 (34)	1			
Yes	32/78 (41)	1.3 (0.7–2.5)	0.80		
Unknown	3/7 (43)	1.5 (0.3–7.1)	0.76		
Number of N1 at primary surgery (n = 110)					
≤10 N1	27/78 (35)	1			
>10 N1	14/32 (44)	1.5 (0.6–3.4)	0.37		
Number of N1-ECE at primary surgery (n = 38)					
≤3	11/24 (46)	1			
>3	8/14 (57)	1.6 (0.4–5.9)	0.50		
LNR at primary surgery (n = 102)					
<0.6	17/49 (35)	1			
≥0.6	21/53 (39)	1.2 (0.5–2.8)	0.60		
Tg before reoperation (n = 148)					
<10 ng/mL	27/79 (34)	1			
≥10 ng/mL	28/69 (41)	1.3 (0.7–2.7)	0.42		
Relapse in previously dissected area					
No	20/63 (32)	1			
Yes	27/68 (40)	1.4 (0.7–2.9)	0.98		
Both (dissected and not dissected)	12/25 (48)	2.0 (0.8–5.1)	0.24		
Relapse size					
≤10 mm	9/28 (32)	1		1	
>10 mm	26/50 (52)	2.3 (0.9–6.0)	0.01	1.6 (0.5–4.9)	0.20
Not applicable	24/78 (31)	1.0 (0.4–2.4)	0.17	0.9 (0.3–2.6)	0.40
RAI refractory					
No	22/65 (34)	1			
Yes	37/91 (41)	1.3 (0.7–2.6)	0.39		
Number of N1 at reoperation					
≤10 N1	49/141 (35)	1			
>10 N1	10/15 (67)	3.7 (1.2–11.6)	0.02		

(*Continued*)

Table 3. Continued

Variable	Persistent Disease/ All Patients [N = 59/156 (%)]	Univariate Analysis OR (95% CI)	*P*	Multivariate Analysis OR (95% CI)	*P*
Number of N1-ECE at reoperation					
≤3	46/132 (35)	1			
>3	12/23 (52)	2.0 (0.8–4.8)	0.12		
LNR at reoperation					
<0.17	19/72 (26)	1		1	
≥0.17	40/84 (47)	2.5 (1.3–4.9)	0.007	1.8 (0.8–3.8)	0.29

Clinical disease is indicated by the presence of clinical findings due to thyroid cancer (palpable lymph nodes, dysphonia, dysphagia).

Long-term follow-up after reoperation of the patients with histologically confirmed relapse

After a mean follow-up of 5 years (range, 0.5 to 16), 24 (24%) of the 99 patients initially classified as CR experienced a secondary relapse. The long-term outcome according to each postreoperative response is detailed in Fig. 2(A). Overall, 97 patients (62%) had CR (including 14 who had had further treatments) and 59 (47%) had an incomplete response (9% BIR, 17% SIR, and 12% IndR) [Fig. 2(B)]. Only 83 (53%) patients maintained a CR at last assessment without further treatments, including 8 patients (2 in BIR and 6 IndR) who achieved CR at last assessment due to a spontaneous decline of Tg level in 7 patients or of TgAbs in 1 patient.

Prognostic factors of the patients with histologically confirmed relapse

We first evaluated the risk factors for incomplete response (*i.e.*, BIR, SIR and IndR patients) at the moment of first postreoperation assessment. Results are shown in Table 2. Only age >45 years, aggressive histology, and LNR at primary surgery were independent risk factors of incomplete response at first postreoperation assessment. The risk factors for incomplete response at last assessment are shown in Table 3. Only male sex and aggressive histology were independent risk factors for incomplete response at last assessment.

We analyzed risk factors for secondary relapse (*i.e.*, among patients with CR on the first postreoperative assessment) (Table 4). Male sex, presence of aggressive histology, and >10 N1 at reoperation were independent risk factors of secondary relapse.

Mortality

Eight patients (5%) died of thyroid cancer during follow-up. The risk of death from thyroid cancer was 14% if >45 years of age at diagnosis (*vs* 0.9% if <45 years of age; $P = 0.001$; OR, 16.8; CI, 2.1 to 774.2); 13% if male (*vs* 0.9% if female; $P = 0.003$; OR, 14.3; CI, 1.8 to 661.3); 13% in the presence of aggressive histology (*vs* 2.6% in the absence of aggressive histology; $P = 0.02$; OR, 5.5; CI, 1.0 to 37.3); 45% in the presence of a relapse of >3 cm (*vs* 4.5% in the presence of a relapse of ≤3 cm; $P = 0.001$; OR, 16.5; CI, 2.5 to 134.2); and 9% in the absence of detectable tumor uptake of RAI (*vs* 0% in cases with RAI uptake; $P = 0.02$; OR, ∞; CI, 1.3 to ∞). Owing to the small number of events, no multivariate analysis of the risk factors for death was performed.

Discussion

Efficacy of first or subsequent reoperation for persistent/recurrent disease ranges from 40% to 100% with various criteria for patient selection and various definitions for successful surgery (6–21). A 63% rate of CR after the first reoperation was found in the present study. At last assessment, after a median follow-up of 5 years, CR without further relapses was found in 53% of the patients. Male sex and presence of aggressive histology were independent predictors of incomplete response to treatment (*i.e.*, absence of CR) at both first postreoperation assessment and at last assessment. In addition to male sex and aggressive histology, age >45 years, relapse of >3 cm, and the absence of RAI uptake were associated with thyroid cancer–specific mortality.

Our study presents several limitations: the retrospective design led to a nonuniform follow-up protocol. The Tg assay changed over time but the functional sensitivity was always <1 ng/mL, which was the cut-off used for response classification. The monocentric design from a tertiary cancer center led to selection of a very aggressive tumor population. This is highlighted by a high frequency of aggressive pathology (25%), a high frequency of initial therapeutic neck dissection (43%), and a high mortality rate (5%). We performed surgery with a curative intent, excluding patients with distant metastases and patients with bulky neck disease for whom complete resection could not be achieved. Despite the selection of patients, the frequent use of localizing procedures that may not be applicable in other settings and an experienced surgical team, a CR was achieved in only 63% of cases.

Table 4. Risk Factors for a Secondary Relapse After CR Obtained With the Reoperation

Variable	Second Relapse/ CR After Reoperation [N = 24/99 (%)]	Univariate Analysis OR (95% CI)	*P*	Multivariate Analysis OR (95% CI)	*P*
Age					
<45 y	15/73 (20)	1			
≥45 y	9/26 (34)	2.0 (0.7–5.5)	0.15		
Sex					
Female	11/73 (15)	1		1	
Male	13/26 (50)	5.6 (2.1–15.8)	0.0007	5.2 (1.6–17.2)	0.006
Clinical disease at diagnosis					
No	8/47 (17)	1			
Yes	13/38 (34)	2.0 (0.8–4.9)	0.19		
Unknown	3/14 (21)	1.2 (0.3–4.3)	0.75		
Surgical intention of the initial surgery					
Prophylactic	4/17 (24)	1			
Therapeutic	14/42 (33)	1.6 (0.4–8.1)	0.54		
Unknown	6/40 (15)	0.5 (0.1–3.3)	0.46		
Aggressive histology					
No	14/82 (17)	1		1	
Yes	10/17 (58)	6.9 (2.3–21.3)	0.0007	10.3 (2.6–40.5)	0.009
Tumor size					
≤20 mm	11/59 (18)	1			
21–40 mm	10/25 (40)	2.9 (1.0–8.2)	0.09		
>40 mm	2/7 (29)	1.7 (0.3–10.0)	0.70		
Unknown	1/8 (13)	0.6 (0.1–5.6)	0.36		
Multifocal					
No	5/37 (14)	1			
Yes	18/57 (32)	2.9 (1.0–8.8)	0.20		
Unknown	1/5 (20)	1.6 (0.2–17.4)	0.95		
Bilateral					
No	9/55 (16)	1			
Yes	14/36 (39)	2.6 (1.0–7.0)	0.44		
Unknown	1/8 (13)	2.4 (0.2–23.0)	0.73		
Extrathyroidal invasion					
No	10/47 (21)	1			
Yes	13/48 (27)	1.2 (0.1–13.2)	0.96		
Unknown	1/4 (25)	1.4 (0.5–3.5)	0.76		
Number of N1 at primary surgery					
≤10 N1	13/56 (23)	1			
>10 N1	5/15 (33)	1.7 (0.5–5.7)	0.36		
Not applicable	6/28 (21)	0.9 (0.3–2.7)	0.53		
Number of N1-ECE at primary surgery					
≤3	8/17 (47)	1			
>3	2/7 (29)	1.5 (0.1–3.0)	0.90		
Not applicable	14/75 (19)	0.3 (0.1–0.8)	0.80		
LNR at primary surgery					
<0.6	11/38 (29)	1			
≥0.6	7/28 (25)	0.8 (0.3–2.5)	0.84		
Not applicable	6/33 (18)	0.5 (0.2–1.7)	0.34		
Tg before reoperation					
<10 ng/mL	10/56 (18)	1			
≥10 ng/Ml	12/39 (31)	2.0 (0.8–5.4)	0.93		
Not applicable	2/4 (50)	4.6 (0.6–36.7)	0.25		
Relapse in previously dissected area					
No	8/43 (19)	1			
Yes	11/41 (27)	1.6 (0.6–4.5)	0.87		
Both (dissected and not dissected)	5/15 (33)	2.2 (0.6–8.2)	0.37		
Relapse size					
≤10 mm	4/18 (22)	1		1	
>10 mm	11/27 (41)	2.4 (0.6–7.5)	0.06	3.0 (0.5–18.2)	0.10
Not applicable	9/54 (17)	0.8 (0.2–2.6)	0.15	0.7 (0.1–3.7)	0.13
RAI refractory					
No	11/40 (28)	1			
Yes	13/59 (22)	0.7 (0.3–1.9)	0.53		

(*Continued*)

Table 4. Continued

Variable	Second Relapse/ CR After Reoperation [N = 24/99 (%)]	Univariate Analysis OR (95% CI)	*P*	Multivariate Analysis OR (95% CI)	*P*
Number of N1 at reoperation					
≤10 N1	21/93 (23)	1		1	
>10 N1	3/6 (50)	3.4 (0.6–18.2)	0.14	6.7 (1.4–31.3)	0.01
Number of N1-ECE at reoperation					
≤3	17/87 (19)	1			
>3	7/12 (58)	5.7 (1.6–20.4)	0.006		
LNR at reoperation					
<0.27	9/52 (17)	1			
≥0.27	15/47 (32)	2.2 (0.9–5.8)	0.09		

Alternatively, in contrast to most series, we defined disease status not only by biochemical markers but also with morphologic assessment. Furthermore, we applied dynamic risk assessment with reclassification of patients according to ATA criteria not only postoperatively but also during follow-up (1). A significant proportion of patients had undetectable serum Tg before reoperation, and thus Tg should not be used alone to assess cure. Excluding patients with undetectable serum Tg before reoperation, the rates of CR and BIR at last assessment were not different to what was observed in the whole series of patients (64% and 10%, respectively; data not shown).

Four of the 161 patients undergoing reoperation in our series had false-positive imaging/cytology. Sarcoidosis and inflammatory disease are known as causes of RAI uptake (27). Cytology also can be falsely positive. Measuring Tg in the aspirate fluid can help for the diagnosis of a metastatic lesion, but a low Tg level in the aspirate fluid does not necessarily exclude malignancy (28, 29). These rare situations have to be taken into account before deciding on surgery.

In medullary thyroid cancer (30) the number of N1 is associated with a patient's outcome, and in our series of DTC the presence of >10 N1 at reoperation was an independent risk factor for secondary relapse after an initial CR.

The LNR was an independent risk factor of incomplete response at the first postoperative assessment. This finding underlines the importance of en bloc compartment-oriented dissection and of high-volume surgeons.

During follow-up, 2 patients in BIR and 6 patients in IndR achieved CR without any additional treatment, as observed after initial treatment (31–34). This phenomenon corresponded to the spontaneous decrease of Tg level in 8 patients or a decrease in TgAbs in 1 patient that may be related to a delayed effect of RAI treatment.

The "response to initial therapy assessment" (1, 34) is more effective than initial risk classification to predict patient outcome. Achieving an "excellent response" after primary treatment can lower the risk of recurrence from 36% to 43% to 2% to 3% in intermediate-risk patients and from 65% to 14% in high-risk patients (34). In our series, roughly a quarter of the 99 patients classified in CR after reoperation relapsed during follow-up. These findings highlight how the "response to initial therapy assessment" might underevaluate the risk of relapse in the setting of a reoperation for persistent/recurrent disease.

Metastatic lesions can be very close to or infiltrate neck structures or can be localized in already dissected areas where extensive scarring can be present. Such lesions are often referred to surgery, but in this setting reoperation carries an increased risk of permanent complications (9, 19, 20). The rate of complications of the reoperation in our cohort was low (≈9%) and comparable to other published series (from 3% to 28%) (9, 14, 19, 20). Nevertheless, 1 patient died of a compressive hematoma. This patient was referred to reoperation because of a 3-cm relapse of tall cell PTC variant, 33 years after initial treatment. The rate of permanent complications after the first thyroid surgery of patients referred to our center was indeed much higher (15% of hypoparathyroidism and 13% of laryngeal paralysis).

International guidelines recommend reoperation for threatening or macroscopic lesions (1). A careful clinical and imaging follow-up strategy can also be adopted for nonthreatening lesions (2–4). A balance between risk and benefits of reoperative surgery should guide surgery decision making with the support of a multidisciplinary team (1). The decision making process should always be shared with the patient. For patients with small, nonthreatening and nonprogressive lesions the risk of permanent side effects can outweigh the benefits of reoperation and a more conservative approach could be the best choice. Alternatively, surgery still represents an opportunity to achieve CR, even for patients with large, progressive, and RAI refractory

recurrent/persisent disease. Increased awareness of risk factors for incomplete response to treatment will help clinicians in their clinical practice.

Conclusion

The rate of CR after first reoperation for persistent/recurrent DTC was 63% at first assessment and 53% at the last assessment after a median of 5 years. Factors for incomplete response after first reoperation were male sex and aggressive histopathological subtype. Following CR, a second relapse was observed in 24% of the patients. Male sex, aggressive histology, and >10 N1 at reoperation were independent risk factors for secondary relapse.

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